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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,788	03/22/2004	Steven C. Quay	03-04US	9945

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EXAMINER	
HEARD, THOMAS SWEENEY	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
01/30/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/805,788	QUAY ET AL.	
	Examiner	Art Unit	
	THOMAS S. HEARD	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-8, 12, 16, 20-28* is/are pending in the application.

4a) Of the above claim(s) *3-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,12,16 and 20-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/27/2008 has been entered.

The Applicants Amendments to the claims received on 10/27/2008 is acknowledged. The text of those sections of Title 35 U.S. Code not included in the action can be found in the prior office action. Rejections or objections not addressed in this office action with respect to the previous office action mailed 3/28/08 are hereby withdrawn.

Claim(s) 3-8, 12, 16, 20-28 are pending. Applicants have amended claim(s) 8, 12, and 16. Claims 3-7 are withdrawn. Claims 8, 12, 16, 20-28 are hereby examined on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

For the purpose of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. V. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held in accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976);In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

Claims 8, 12, 16, and 20-28 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Armour Pharmeceutical Company (EP 0115627) referred to as APC, and Moise Azria et al U.S. Patent 5,759,565, both from Applicant's IDS and made of record in th previous office action, and Grebow et al US Patent 5,026,825.

In instantly claimed invention is drawn to a composition comprising: an aqueous solution of calcitonin salmon at a concentration of 0.0355% w/w or 2,200 International Units (I.U.) per ml; Chlorobutanol at a concentration of about 0.25% to about 0.4% weight/weight; sodium chloride at a concentration of 0.85% weight/weight; a pH between 3 to 4; less than 5% oxygen; wherein the composition is suitable for intranasal administration in humans.

Azria et al teaches calcitonin in a saline solution (tonicity) of 0.75 % w/w which is about 0.85%, and at a pH of 3 to 5, see Claims 1 and 18 of Azria et al for example. The composition(s) taught are for nasal administration. The amount of calcitonin used in the invention is taught to be between 150 and 8,000 MRC units (I.U. of Activity) of salmon calcitonin, readable on Applicant's 2200 I.U. per ml. The composition is taught to be to be stored under an inert Nitrogen atmosphere (an oxygen depleted environment) for stability of the calcitonin. Chlorbutanol is also taught as being use in the nasal composition but suffers from some drawbacks when used at concentrations above 0.6%. Azria et al does not teach the use of Chlorbutanol at ranges instantly claimed. The difference between what is taught by Azria et al and that of the prior art is Azria teaches that concentration of chlorobutanol above 0.6% have undesired effects but does not teach concentration ranges of chlorobutanol of between about 0.25% to 0.4% w/w.

APC teaches pharmaceutical composition for nasal administration comprising calcitonin at a concentration range from 1 to 150 µg/ml where the concentration and dosage levels of calcitonin are with a potency of about 4000 I.U. per mg, well within the range taught by Azria et al and instantly claimed. APC teaches the use of a Tonicity Adjuster in the range of 0.01-0.5 %w/v readable upon the saline solution of Azria et al. APC also teaches the use of Chlorobutanol (a preservative) in the range of 0.001-2.0 % w/v which is in the range instantly claimed, see page 5 and line 5-18 and page 6 for the additive ranges; note that the examiner is taking the mass of water to be 1 g/ml

therefore which makes the translation fro w/v% to be essentially identical to that of w/w%.

Grebow et al, US Patent 5,026,825 teaches an intranasal composition comprising from about 0.0001% W/V to about 15% W/V of a polypeptide salmon calcitonin or a polypeptide having calcitonin activity (potency of from about 100 to about 10,000 international units per mg of polypeptide readable upon Applicant 0.355% w/w of Claim 8 and 2200 I.U of Claim 12 and 16, see Claims 1-7 of '825. Grebow further teaches the preservative Chlorobutanol in ranges from 0.5-1.0 and in Example 9, teaches Chlorobutanol at 0.1% w/v. Note that the examiner is taking the mass of water to be 1 g/ml therefore which makes the translation fro w/v% to be essentially identical to that of w/w%. Further note that while Grebow teaches ranges from 0.5-1.0 %w/v. in column 12, but has a specific example using 0.1% w/v, which makes the effective range 0.1-1.0% readable on the instant ranges claimed.

It would have been obvious at the time of the instantly claimed invention to use concentrations of chlorobutanol as a preservative at %w/v concentrations below that of 0.6% to prevent any deleterious effects in the composition as the art clearly teaches the use of Chlorobutanol in combination with calcitonin, and at concentrations as low as 0.1% w/v as taught by Grebow et al. The prior art references clearly shows the use of chlorobutanol in combination with calcitonin and at the pH ranges instantly claimed. It would have been obvious to one skilled in the art at the time of invention to determine all operable and optimum components in the claimed composition of U.S. Patent No. Armour Pharmeceutical Company (EP 0115627) and Moise Azria et al U.S. Patent

5,759,565, because the component % w/v are an art-recognized result-effective variable that is routinely determined and optimized in the composition arts. One would have been motivated to modify the composition as taught by both APC, Azria et al, and Grewbow to optimize the concentration parameters to eliminate undesirable effect of any given component and or enhance the effect of a given component as calcitonin, saline, Chlorobutanol, as the art teaches both their combination and use, and within the ranges instantly claimed. While the prior art is silent on the composition being at less than 5% oxygen, it is the Examiner's position that oxygen would be less than 5% in the composition(s) taught by the art because oxygen is quite insoluble and envisioning even the upper end of 5% (5g of 0_2 per 100 ml of water) is rather difficult. The storing of the compositions under inert condition (under a Nitrogen atmosphere) is readable upon having the O_2 concentration below 5%, if not totally eliminating the presence of O_2. Given the intended use of the composition is for nasal administration, putting the composition into a sprayer is obvious and readable upon Claims 20-28. The parameters of the actuator tip, spray pattern, droplet size etc... are also art-recognized result-effective variables that are routinely determined and optimized for nasal administration in the composition arts. The limitations of Claims 20-28 are a function of the applicator and do not have patentable weight on the composition itself. Just because the device can spray at a particular angle and produce droplets of a certain size does not alter the composition over the prior art because the device will spray any liquid at those desired angles and droplet size. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation

of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection. Applicants have argued again the Azria et al reference teaches away from the use of chlorobutanol and would "chill" the motivation of the ordinary worker to turn to another reference that also taught chlorobutanol. It is further argued that it is the Examiner's position that the skilled worker would then be motivated to rely upon the APC and Grebow reference to optimize the effects of any given component. If it finally argued:

> As noted above, Azria taught use of calcitonin solutions comprising either benzalkonium chloride or a surfactant. One of ordinary skill cannot be motivated to "trade- off" the advantages of one reference to combine with another (see Winner Int'l Royalty Corp. v. Wang, 53 USPQ2d 1580, 1587 (Fed. Cir. 2000). Here, Examiner improperly argued that one of ordinary skill would ignore the advantages taught and claimed by Azria, which required solutions with either benzalkonium chloride or a surfactant, while combining the teachings of Azria with those of APC and Grebow to arrive at Applicant's claimed invention, which required neither benzalkonium chloride nor a surfactant. Moreover, both APC and Grebow required a surfactant or A-aminolevulinic acid, respectively. Apparently, the advantages taught by Azria were appreciated and adopted by APC and Grebow. An ordinary skilled worker would not "trade-off" underscored advantages that were described and claimed by Azria when combining with APC or Grebow or both. Accordingly, Examiner's alleged motivation to combine requires trading off the advantages taught in Azria and incorporated into APC and Grebow. For these reasons is a motivation to combine Azria with APC and Grebow is lacking.

Applicants have focused on the Aria et al article throughout the prosecution history, and solely because of the teaching of chlorobutanol concentrations above 0.6% have undesired effects. Because Azria et al does teach the skilled artisan that the

concentration of chlorobutanol can have undesired effects above a given %w/v or %w/w, this teaching does not "chill" the motivation to use chlorobutanol but rather to use it below a given %w/v or %w/w value. All three references used in the rejection supra teach calcitonin and chlorobutanol together in a composition. Two of the references do not teach that the use of chlorobutanol is problematic. Thus, the combination of all three references would teach the skilled artesian that chlorobutanol is to be used as a preservative, but the concentration of chlorobutanol should be kept below 0.6% to prevent or minimize the destructive properties to the rubber stopper. Because a given component of a composition can have undesired effects at a given concentration does not teach away from the use of that component, but rather an optimization to provide the benefit without the undesired effect(s). Thus, the teaching of an upper limit on a given component is not teaching away from the use of chlorobutanol in its entirety. Since untold number of compounds used in today's pharmaceutical compositions can have undesired effects above certain concentrations, if these undesired effects were a teach away, then hardly any drugs would be on the market.

Finally, regarding the argument that one of ordinary skill cannot be motivated to "trade- off" the advantages of one reference to combine with another (see Winner Int'l Royalty Corp. v. Wang, 53 USPQ2d 1580, 1587 (Fed. Cir. 2000). The prior art rejections made with the combination of references were not directed to a tradeoff between a surfactant, benzalkonium chloride, or A-aminolevulinic acid, as argued supra. The Examiner focused solely on the combinations of chlorobutanol, calcitonin, the pH, and the % oxygen, i.e., the material claimed. The Examiner did not address any tradeoff

or differences between surfactant, benzalkonium chloride, or A-aminolevulinic acid in the rejection, nor in response to Applicant's arguments throughout the prosecution history, but only whether the components instantly claimed were ever used in combination with one another. Therefore, the assertion that the Examiner's alleged motivation to combine requires trading off the advantages taught in Azria and incorporated into APC and Grebow is inaccurate to the reasoning and rational of the rejection. Therefore, the rejection is maintained for reasons of record.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Prior art contained in the reference of record can be applied in the next office action.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas S. Heard whose telephone number is (571) 272-2064. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anish Gupta/
Primary Examiner, Art Unit 1654

/Thomas S Heard/
Examiner, Art Unit 1654